

In vitro modeling of human motor neuron disease

Grant Award Details

In vitro modeling of human motor neuron disease

Grant Type: Basic Biology V

Grant Number: RB5-07480

Project Objective: To develop in vitro stem cell based systems to biologically probe motor neuron (MN) diseases such as spinal muscular atrophy (SMA) and amyotrophic lateral sclerosis (ALS). By establishing a novel cell culture platform in which the activity of stem cell-derived MNs can be assessed using a combination of classical electrophysiological approaches in concert with newly developed light-based (optogenetic) stimulation and recording techniques, the lab hopes to advance both the biological understanding of these diseases as well as evaluate current therapeutic approaches .

Investigator:

| | |
|---------------------|---------------------------------------|
| Name: | Bennett Novitch |
| Institution: | University of California, Los Angeles |
| Type: | PI |

Disease Focus: Neurological Disorders, Spinal Muscular Atrophy

Human Stem Cell Use: iPS Cell

Award Value: \$1,148,758

Status: Active

Progress Reports

Reporting Period: Year 1

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Reporting Period: Year 2

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Reporting Period: Year 3

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Reporting Period: Year 4 (NCE)

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Grant Application Details

Application Title: In vitro modeling of human motor neuron disease

Public Abstract: Motor neuron (MN) diseases such as spinal muscular atrophy and amyotrophic lateral sclerosis lead to progressive degeneration of MNs, presenting first with muscle weakness, followed by locomotor defects and frequently death due to respiratory failure. While progress has been made in identifying genes associated with MN degeneration, the molecular and cellular processes underlying disease onset and progression remain unclear, and no effective therapies are available. Methods to direct the development of normal and diseased motor neurons from human embryonic and induced pluripotent stem cells have recently been developed, raising hope that these cells could offer a means for investigating the root causes of MN disease and devising screens for neuroprotective agents. Most stem cell-based disease modeling efforts have thus far focused on the issue of MN survival at the end stages of disease progression. However, studies in animal models and human patients indicate that MN function declines well before MN death is prevalent. We have developed a simple, yet physiologically relevant platform for measuring the activity of normal and diseased human MNs and muscle cells in a manner that has not previously been possible. Here we propose to explore how MN function declines; eventually we hope to test new therapeutics. These studies provide a crucial bridge between studies of motor circuit function in animal models and the molecular and cellular tools available to study cells in culture.

Statement of Benefit to California: Neurological diseases are among the most debilitating medical conditions that affect millions of Californians each year, and many more worldwide. Few effective treatments for these diseases currently exist, in part because we know very little about the mechanisms underlying these conditions. Through the use of human embryonic stem cell and induced pluripotent stem cell technologies, it is now possible to create neurons from patients suffering from a variety of neurological disorders that can serve as the basis for cell culture-based models to study disease pathologies. Our proposed research specifically seeks to develop an innovative system for investigating the early stages of neuromuscular disease onset and progression in an experimentally accessible cell culture setting. The generation of this model will constitute an important step towards understanding the root cause of neurological dysfunction and developing a platform for the discovery of drugs that can alter disease outcomes and improve the productivity and quality of life for many Californians. Moreover, progress in this field will help solidify the leadership role of California in bringing stem cell research to the clinic, and stimulate the future growth of the biotechnology and pharmaceutical industries within the state.

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